20020128.0726

FIG. 1

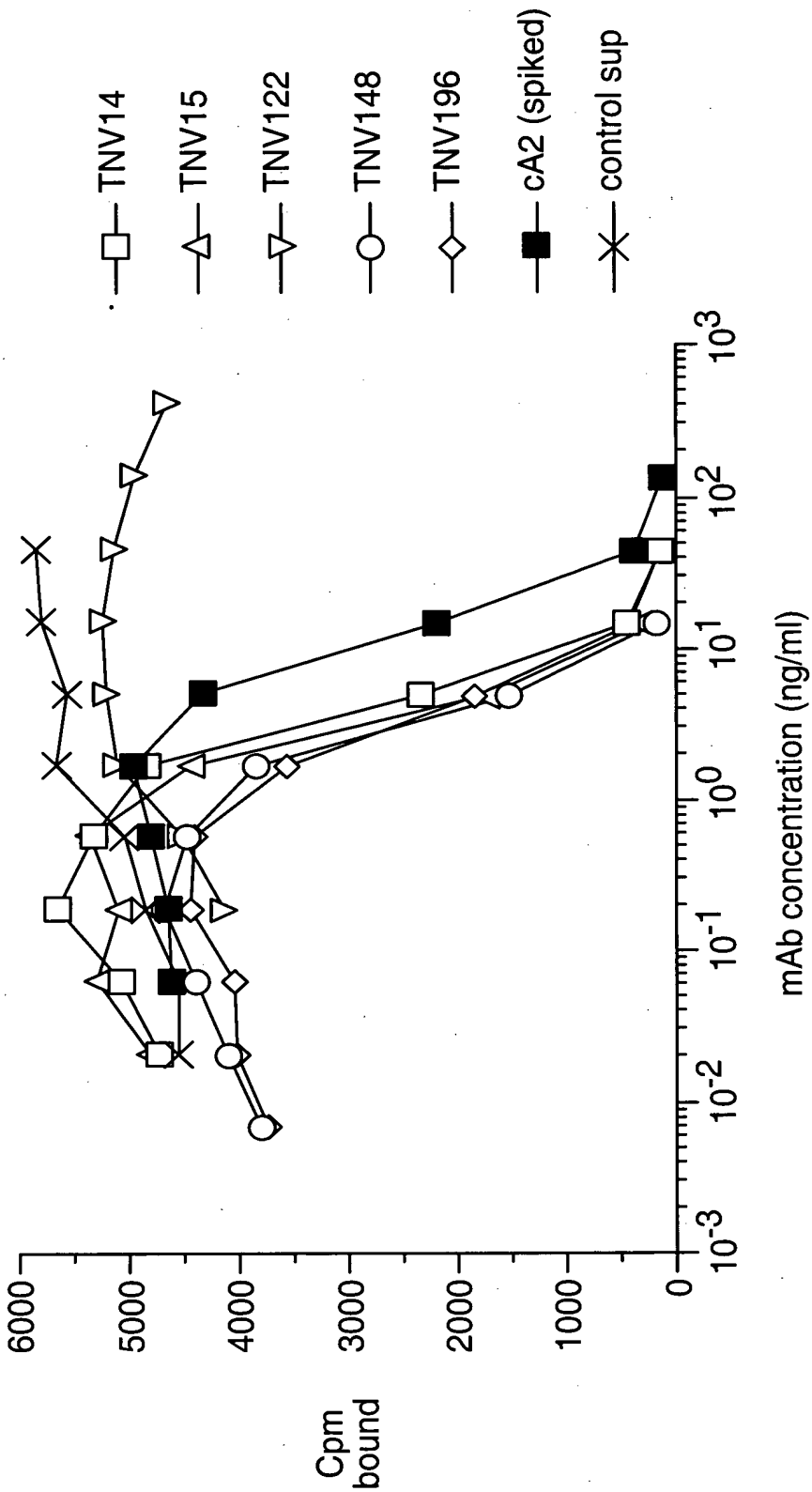


FIG. 2A

```
TNVs        ATGGGGTTTGGGCTGAGCTGGGTTTTCCTCGTTGCTCTTTTAAGA

                              Q  V  Q  L  V  E  S  G  G  G  V
germline                   CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTG
TNVs        GGTGTCCAGTGT.....................................
TNV148(B)   GGTGTCCAGTGT.....A...............................

             V  Q  P  G  R  S  L  R  L  S  C  A  A  S  G
germline    GTCCAGCCTGGGAGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGA
TNVs        .....................................................

             F  T  F  S  S  Y  A  M  H  W  V  R  Q  A  P
germline    TTCACCTTCAGTAGCTATGCTATGCACTGGGTCCGCCAGGCTCCA
TNV14,15    .....................................................
TNV148(B)   ....T................................................
TNV196      ....................C................................

             G  K  G  L  E  W  V  A  V  I  S  Y  D  G  S
germline    GGCAAGGGGCTGGAGTGGGTGGCAGTTATATCATATGATGGAAGC
TNV14       ........................A....C.T...........T
TNV15       ........................T.....T...........T
TNV148(B)   .....C..................T....G..............
TNV196      ........................T....................

             N  K  Y  Y  A  D  S  V  K  G  R  F  T  I  S
germline    AATAAATACTACGCAGACTCCGTGAAGGGCCGATTCACCATCTCC
TNV14       .GC...A.G.....G............A.................
TNV15       ..C...A.G.....................C.............
TNV148(B)   ......A.G.....................................
TNV196      ......A.G.C.............................G.....
```

5,985,553

FIG. 2B

```
                 R  D  N  S  K  N  T  L  Y  L  Q  M  N  S  L
germline   AGAGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTG
TNV14      ...............................................
TNV15      ..................G............................
TNV148     .........C.....................................
TNV148B    ...............................................
TNV196     ........................T......................

                R  A  E  D  T  A  V  Y  Y  C  A  R
germline   AGAGCTGAGGACACGGCTGTGTATTACTGTGCGAGA
TNV14,15   ..................................GATCGAGGT
TNV148(B)  ...........................................A
TNV196     ......................T........................

                                   Y  Y  Y  Y  Y  G  M  D  V  W
germline                          TACTACTACTACTACGGTATGGACGTCTGG
TNV14
ATATCAGCAGGTGGAA.....................
TNV15
G.C............A.T..T.....................
TNV148(B)  ...G..........A..............................
TNV196     ..TGG.........A..............................

               G  Q  G  T  T  V  T  V  S  S
germline   GGGCAAGGGACCACGGTCACCGTCTCCTCAG
TNV14            ..C.............................
TNV15            ..C.............................
TNV148(B)  ..C..........................
TNV196     ..C..G..................
```

FIG. 3

```
TNVs        ATGGAAGCCCCAGCTCAGCTTCTCTTCCTCCTGCTACTCTGGCTC

                                E  I  V  L  T  Q  S  P  A  T
germline                      GAAATTGTGTTGACACAGTCTCCAGCCACC
TNVs        CCAGATACCACCGGA.............................

             L  S  L  S  P  G  E  R  A  T  L  S  C  R  A
germline    CTGTCTTTGTCTCCAGGGGAAAGAGCCACCCTCTCCTGCAGGGCC
TNVs        ...........................................

             S  Q  S  V  S  S  Y  L  A  W  Y  Q  Q  K  P
germline    AGTCAGAGTGTTAGCAGCTACTTAGCCTGGTACCAACAGAAACCT
TNV14,15    ...........................................
TNV148,196
     ...........TA.....................................

              G  Q  A  P  R  L  L  I  Y  D  A  S  N  R  A
germline    GGCCAGGCTCCCAGGCTCCTCATCTATGATGCATCCAACAGGGCC
TNVs        ...........................................

              T  G  I  P  A  R  F  S  G  S  G  S  G  T  D
germline    ACTGGCATCCCAGCCAGGTTCAGTGGCAGTGGGTCTGGGACAGAC
TNVs        ...........................................

              F  T  L  T  I  S  S  L  E  P  E  D  F  A  V
germline    TTCACTCTCACCATCAGCAGCCTAGAGCCTGAAGATTTTGCAGTT
TNVs        ...........................................

             Y  Y  C  Q  Q  R  S  N  W  P  P  F  T  F  G
Germline      TATTACTGTCAGCAGCGTAGCAACTGGCCTCCATTCACTTTCGGC
TNVs        ...........................................

             P  G  T  K  V  D  I  K  R
gerline     CCTGGGACCAAAGTGGATATCAAACGT
TNVs        ...........................
```

FIG. 4

```
      germline  MGFGLSWVFLVALLRGVQC                          signal
TNVs            ...................

germline  QVQLVESGGGVVQPGRSLRLSCAASGFTFS                     FR1
TNVs      ............................
TNV148(B) ........................I..

germline  SYAMH                                              CDR1
TNVs      .....

germline  WVRQAPGKGLEWVA                                     FR2
TNVs      ..............
TNV148(B) .......N......

germline  VISYDGSNKYYADSVKG                                  CDR2
TNV14           I.L....S.K......D
TNV15           F.L......K.......
TNV148(B) FM.......K.......
TNV196    F........KS......

germline  RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR                   FR3
TNV14           ................................
TNV15           ...........A....................
TNV148    ........P.......................
TNV148B   ................................
TNV196    ...V.........F.............F....

germline  --------YYYYYGMDV
TNV14           DRGISAGGN........                           CDR3
TNV15           ...V....N........
TNV148(B) ....A...N........
TNV196    ....G...N........

germline  WGQGTTVTVSS                                       J6
TNVs      ...........
```

FIG. 5

TNVs	MEAPAQLLFLLLLWLPDTTG	**signal**
germline	EIVLTQSPATLSLSPGERATLSC	**FR1**
TNVs	.....	
germline	RASQSVSSYLA	**CDR1**
TNV14	.....	
TNV15	.....	
TNV148(B)	.....Y....	
TNV196	.....Y....	
germline	WYQQKPGQAPRLLIY	**FR2**
TNVs	.....	
germline	DASNRAT	**CDR2**
TNVs	.....	
germline	GIPARFSGSGSGTDFTLTISSLEPEDFAVYYC	**FR3**
TNVs	.....	
germline	QQRSNWPPFT	**CDR3**
TNVs	.....	
germline	FGPGTKVDIK	**J3**
TNVs	.....	

FIG. 6

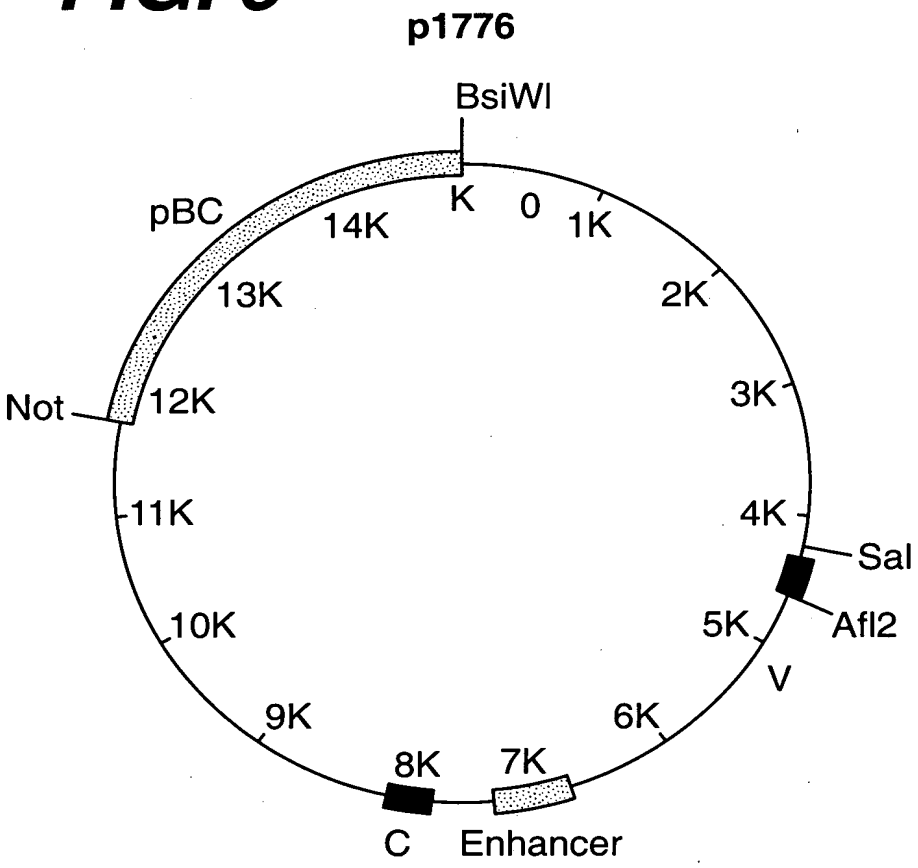
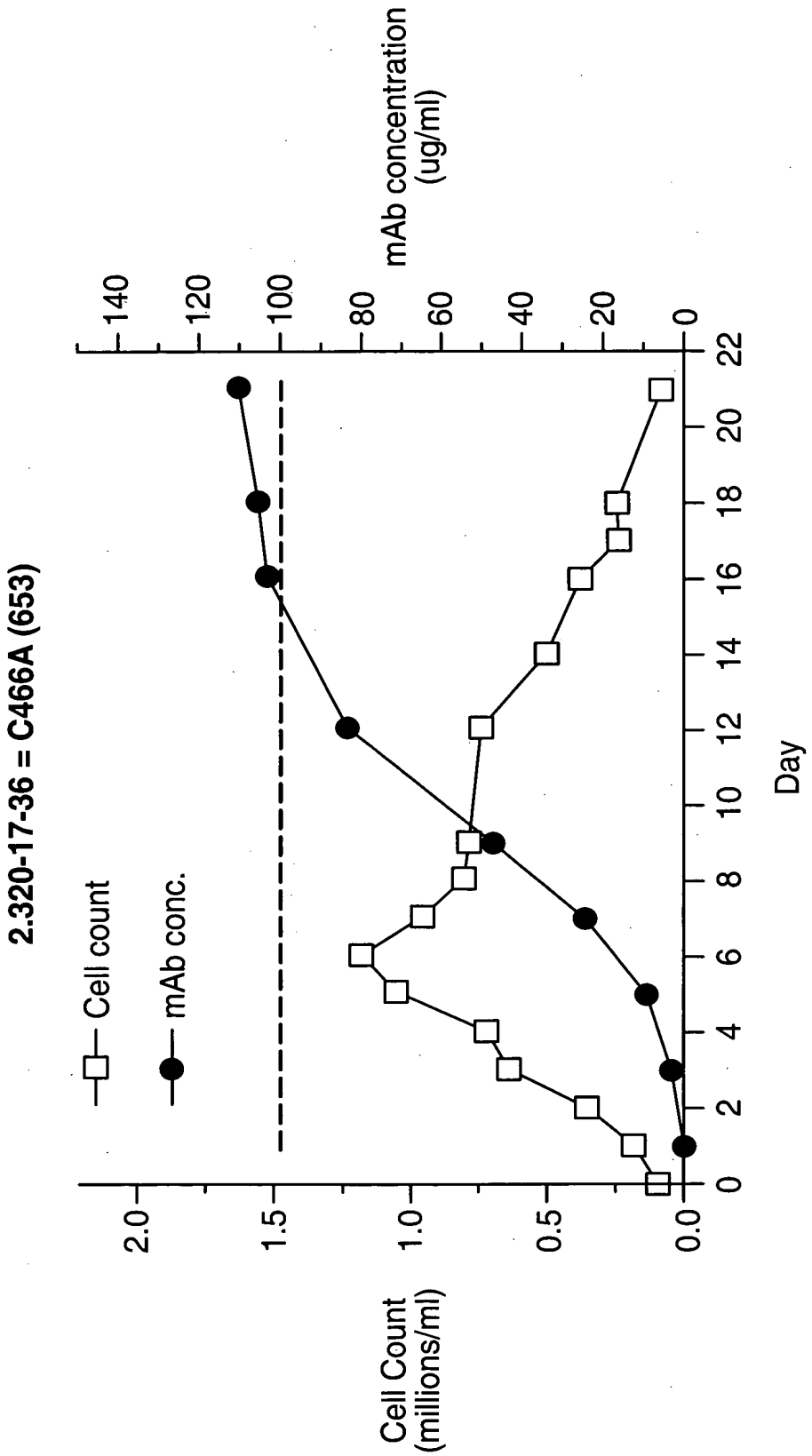
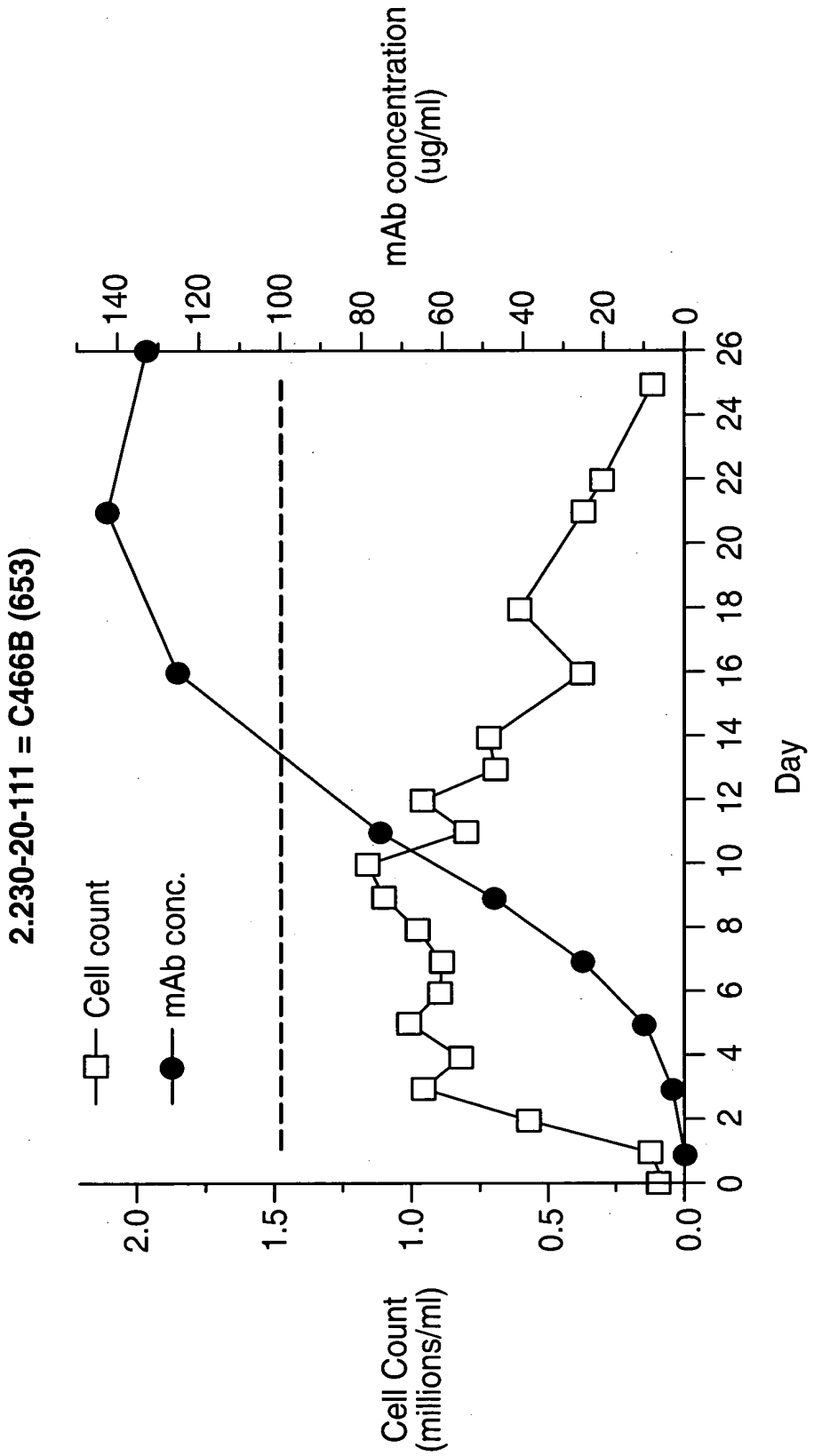

p1776
BsiWI
K
0
1K
2K
3K
4K
Sal
Afl2
5K
V
6K
7K
Enhancer
8K
C
9K
10K
11K
12K
Not
13K
14K
pBC

FIG. 7A


2.320-17-36 = C466A (653)
Cell count
mAb conc.
Cell Count (millions/ml)
mAb concentration (ug/ml)
Day
0.0
0.5
1.0
1.5
2.0
0
20
40
60
80
100
120
140
0
2
4
6
8
10
12
14
16
18
20
22

29855/27626

FIG. 7B



Sheet 10 of 26

FIG. 7C

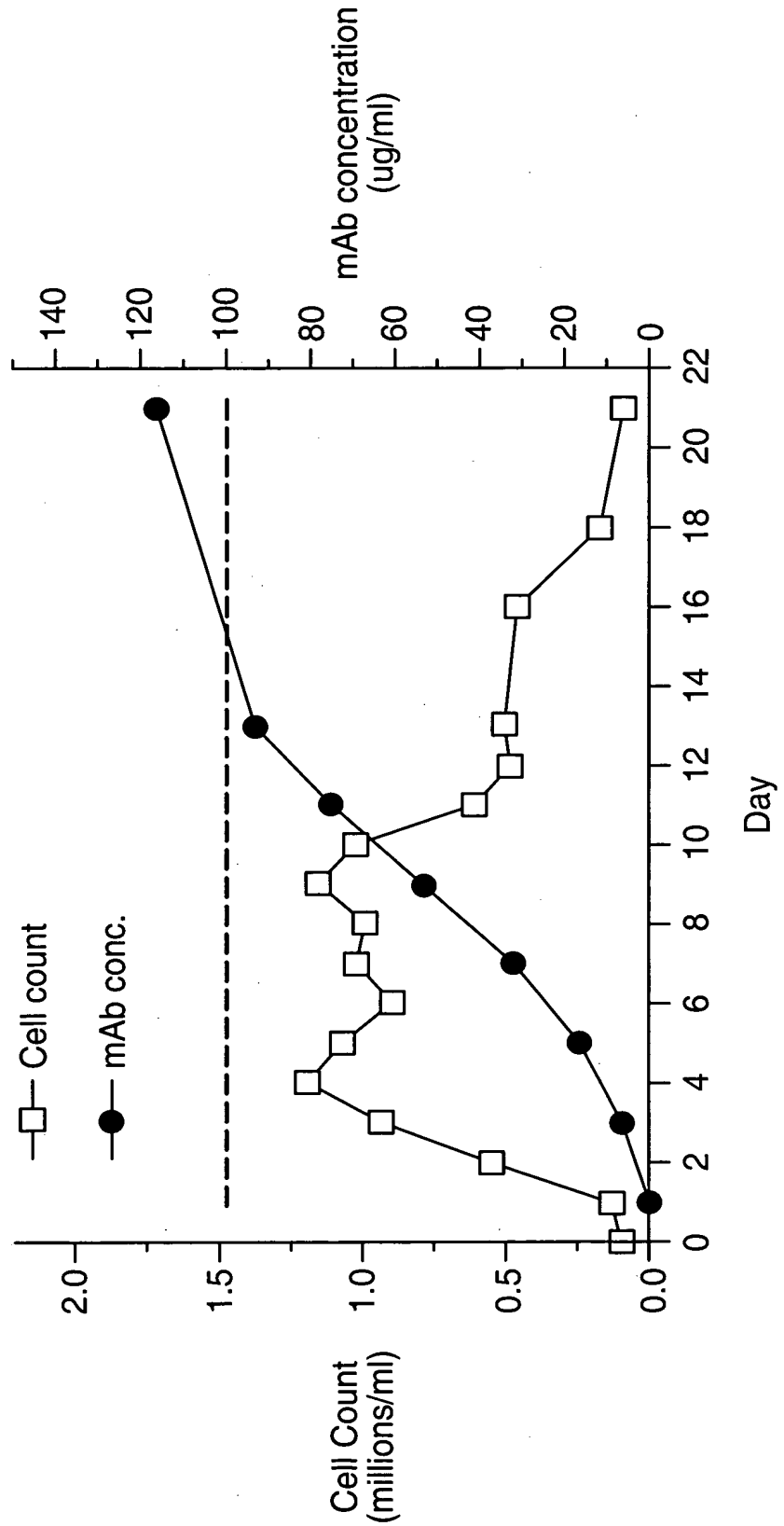


FIG. 7D

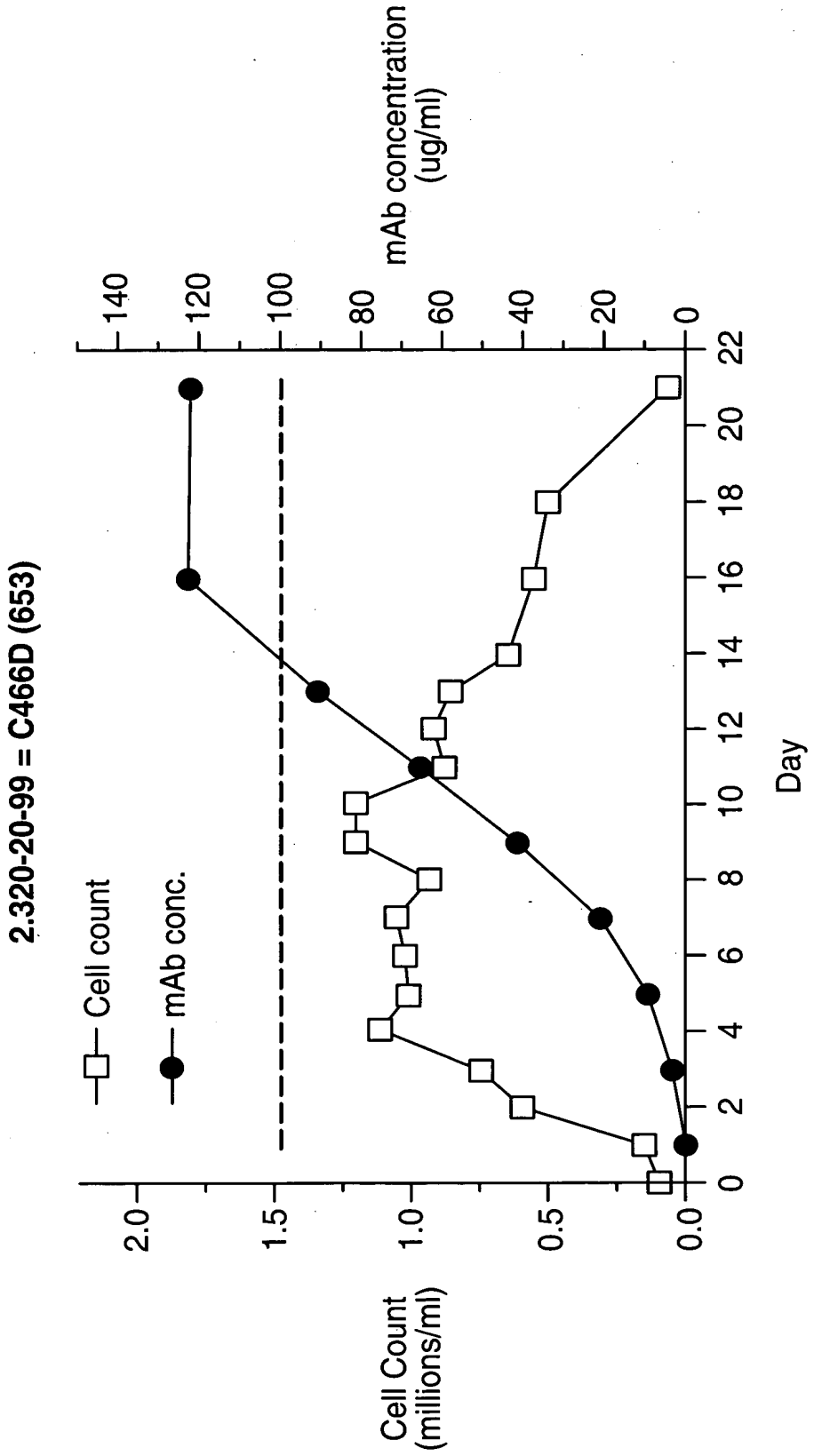

2.320-20-99 = C466D (653)
Cell count
mAb conc.
Cell Count (millions/ml)
mAb concentration (ug/ml)
Day
0.0
0.5
1.0
1.5
2.0
0
20
40
60
80
100
120
140
0
2
4
6
8
10
12
14
16
18
20
22

FIG. 7E

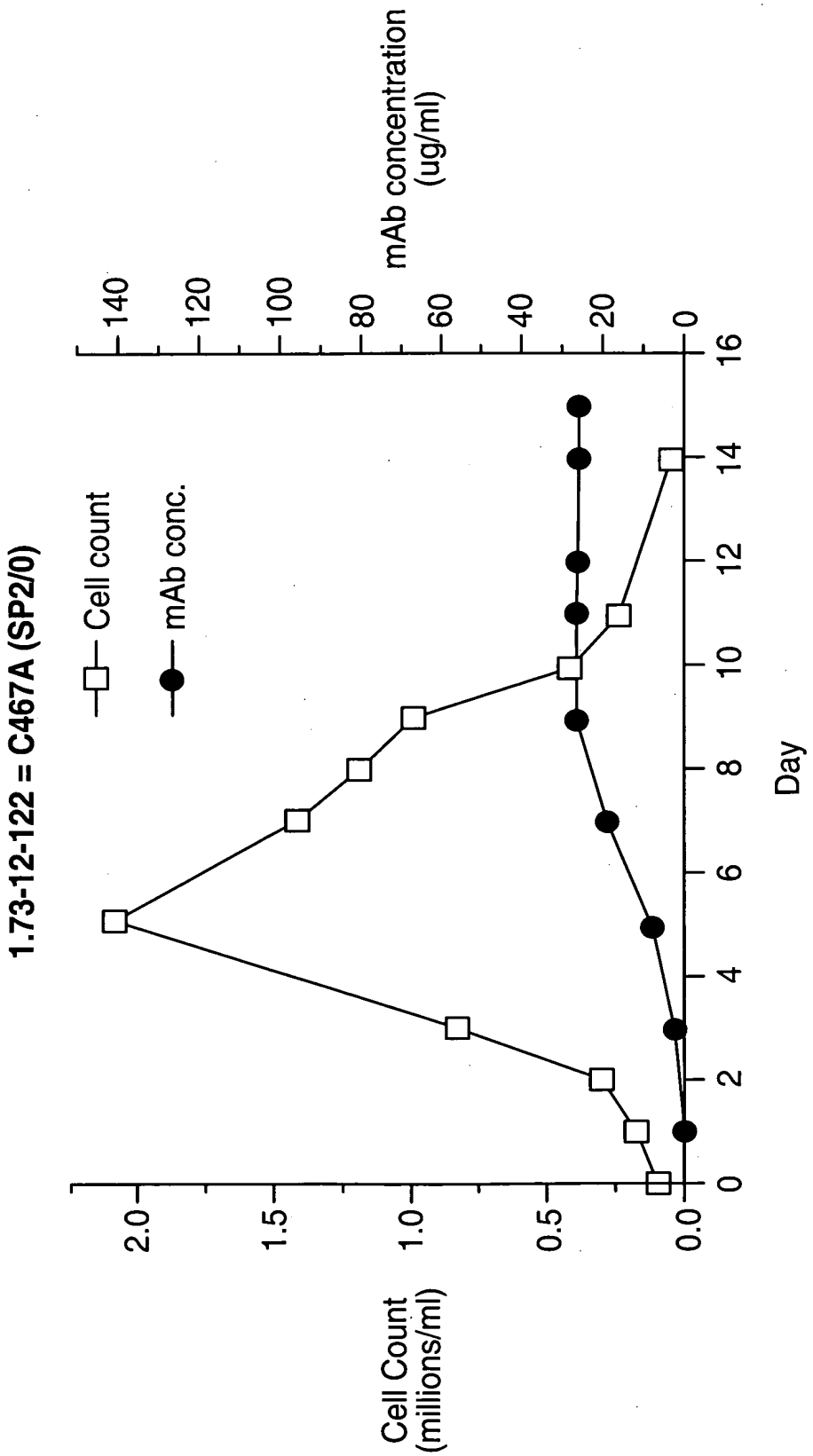

1.73-12-122 = C467A (SP2/0)
Cell count
mAb conc.
mAb concentration (ug/ml)
Cell Count (millions/ml)
Day
0.0
0.5
1.0
1.5
2.0
0
2
4
6
8
10
12
14
16
0
20
40
60
80
100
120
140

FIG. 8

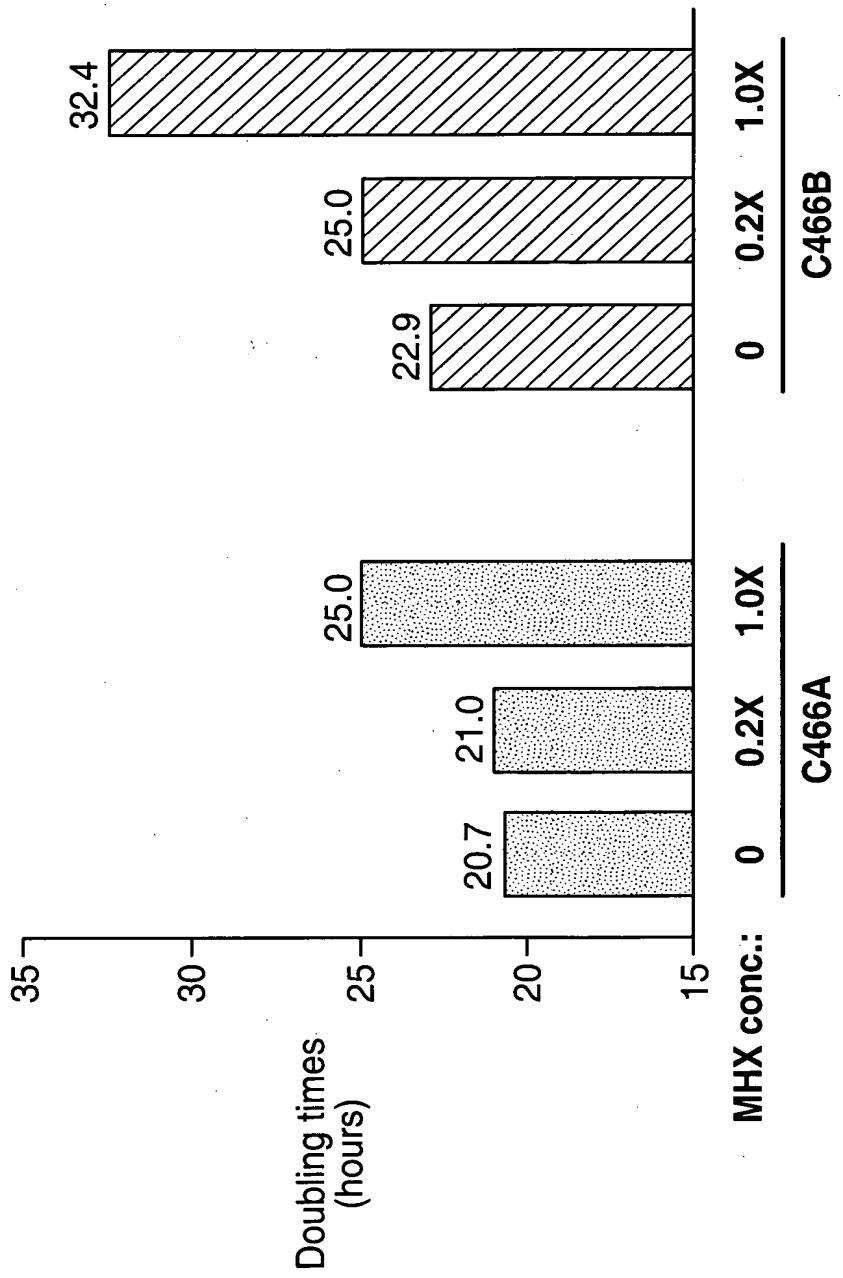

Doubling times (hours)
35
30
25
20
15
20.7
21.0
25.0
22.9
25.0
32.4
MHX conc.:
0
0.2X
1.0X
0
0.2X
1.0X
C466A
C466B

FIG. 9A

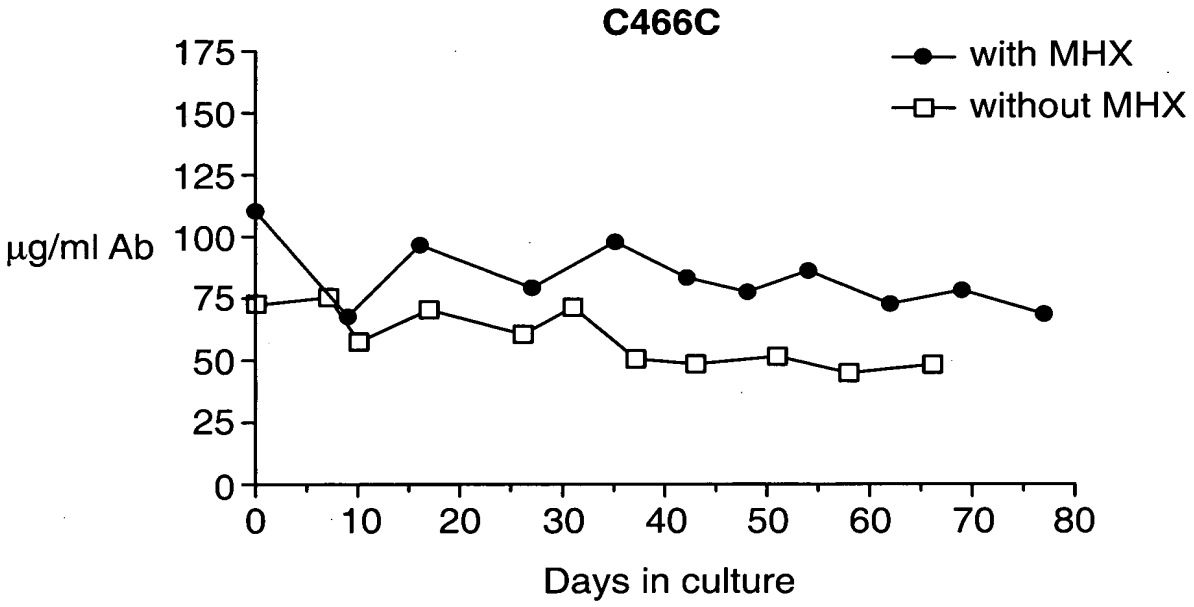

C466C
with MHX
without MHX
µg/ml Ab
175
150
125
100
75
50
25
0
0
10
20
30
40
50
60
70
80
Days in culture

FIG. 9B

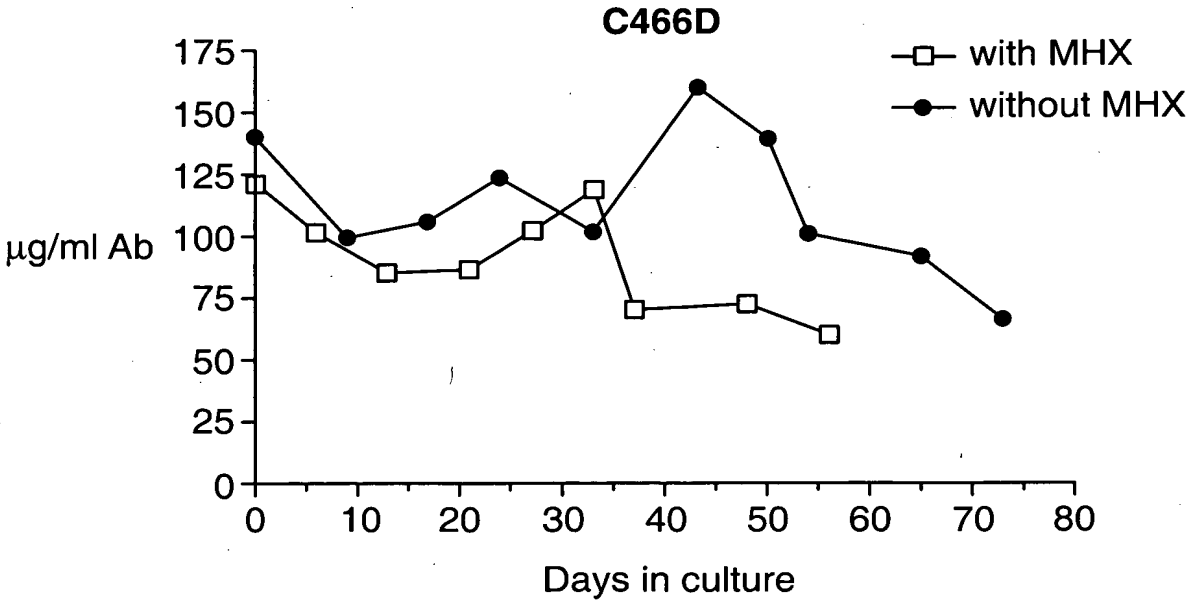

C466D
with MHX
without MHX
µg/ml Ab
175
150
125
100
75
50
25
0
0
10
20
30
40
50
60
70
80
Days in culture

FIG. 10

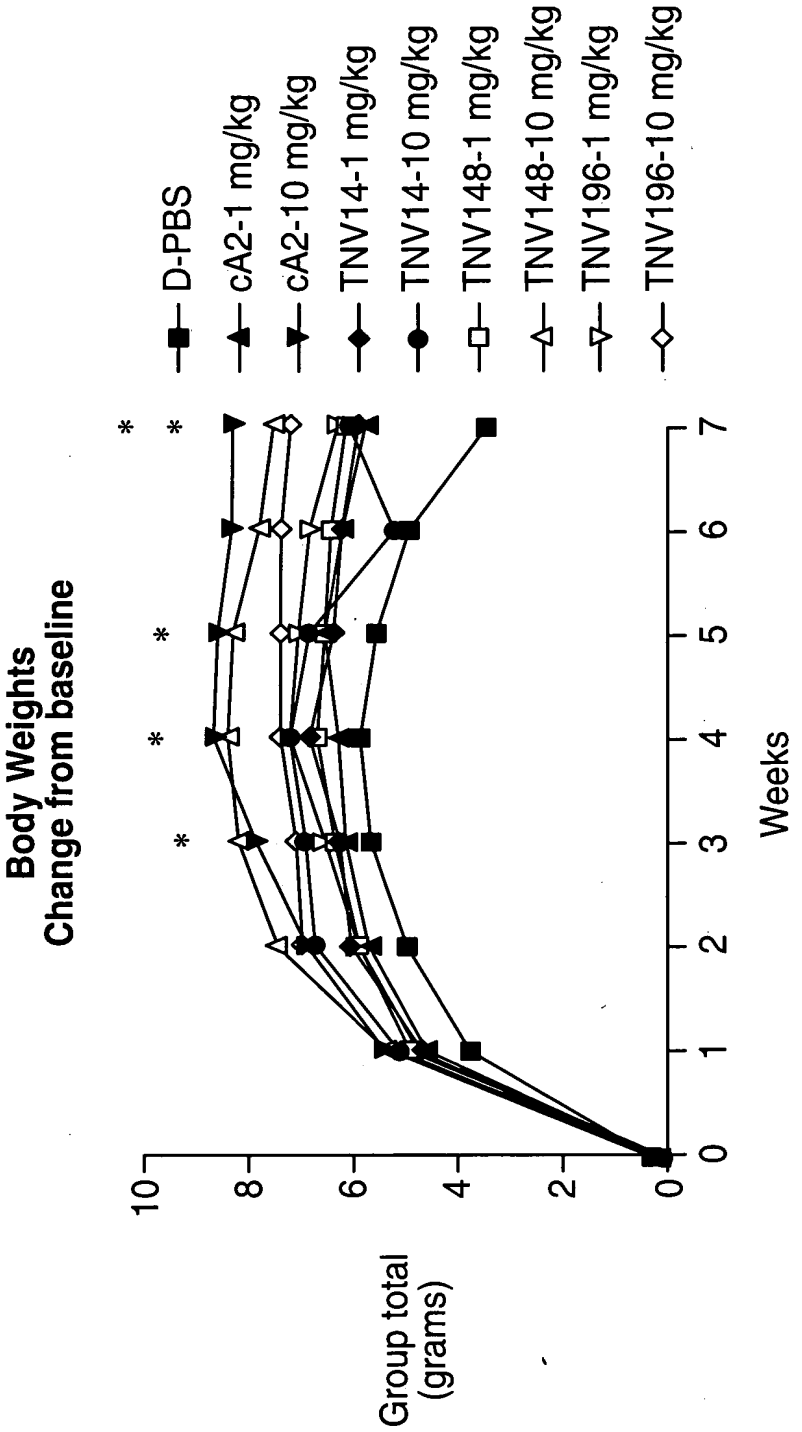

Body Weights
Change from baseline
D-PBS
cA2-1 mg/kg
cA2-10 mg/kg
TNV14-1 mg/kg
TNV14-10 mg/kg
TNV148-1 mg/kg
TNV148-10 mg/kg
TNV196-1 mg/kg
TNV196-10 mg/kg
Group total (grams)
Weeks
0
2
4
6
8
10
0
1
2
3
4
5
6
7
*
*
*
*

FIG. 11A

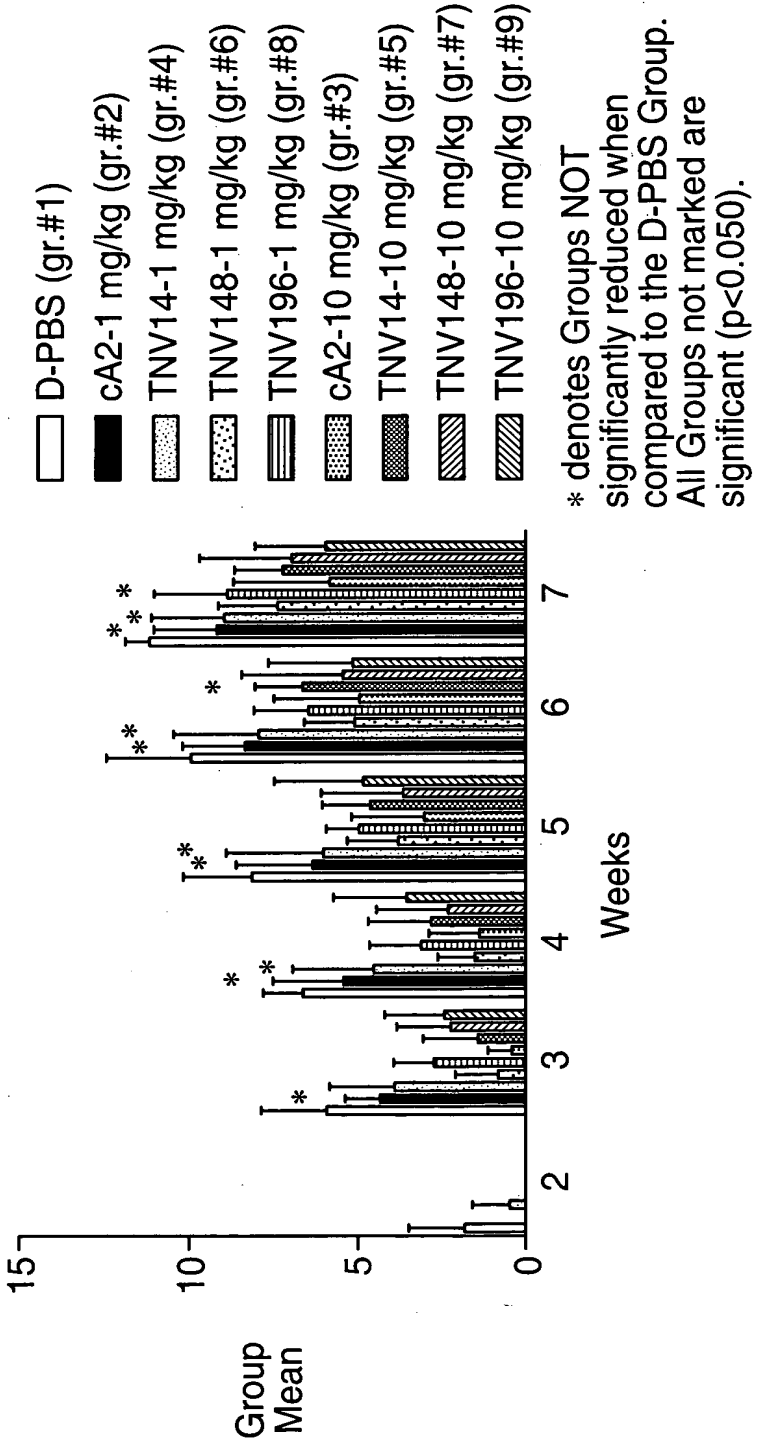

Arthritic Index
Group Mean
15
10
5
0
2
3
4
5
6
7
Weeks
D-PBS (gr.#1)
cA2-1 mg/kg (gr.#2)
TNV14-1 mg/kg (gr.#4)
TNV148-1 mg/kg (gr.#6)
TNV196-1 mg/kg (gr.#8)
cA2-10 mg/kg (gr.#3)
TNV14-10 mg/kg (gr.#5)
TNV148-10 mg/kg (gr.#7)
TNV196-10 mg/kg (gr.#9)
* denotes Groups NOT significantly reduced when compared to the D-PBS Group. All Groups not marked are significant (p<0.050).

FIG. 11B

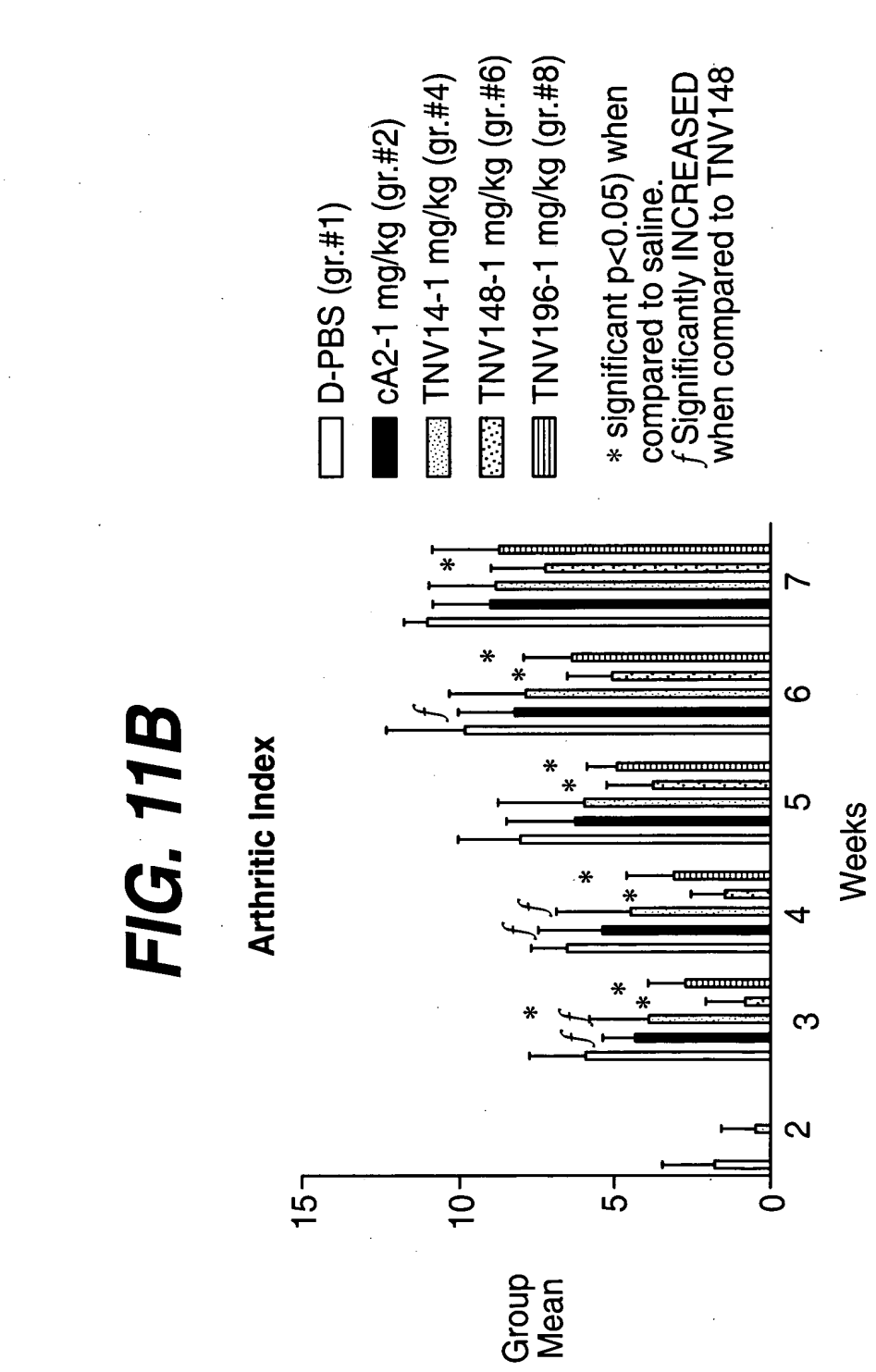

Arthritic Index
D-PBS (gr.#1)
cA2-1 mg/kg (gr.#2)
TNV14-1 mg/kg (gr.#4)
TNV148-1 mg/kg (gr.#6)
TNV196-1 mg/kg (gr.#8)
* significant p<0.05) when compared to saline.
f Significantly INCREASED when compared to TNV148
Group Mean
0
5
10
15
2
3
4
5
6
7
Weeks

FIG. 11C

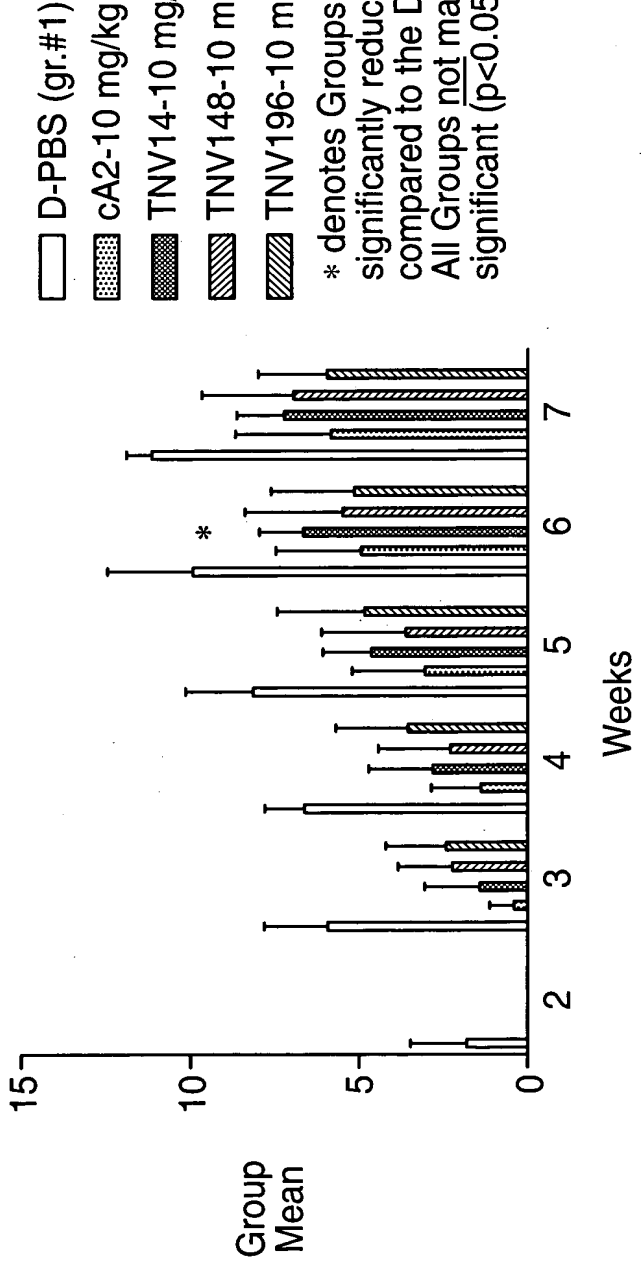

Arthritic Index
D-PBS (gr.#1)
cA2-10 mg/kg (gr.#3)
TNV14-10 mg/kg (gr.#5)
TNV148-10 mg/kg (gr.#7)
TNV196-10 mg/kg (gr.#9)
* denotes Groups NOT significantly reduced when compared to the D-PBS Group. All Groups not marked are significant (p<0.050).
Group Mean
0
5
10
15
2
3
4
5
6
7
Weeks
*

FIG. 12

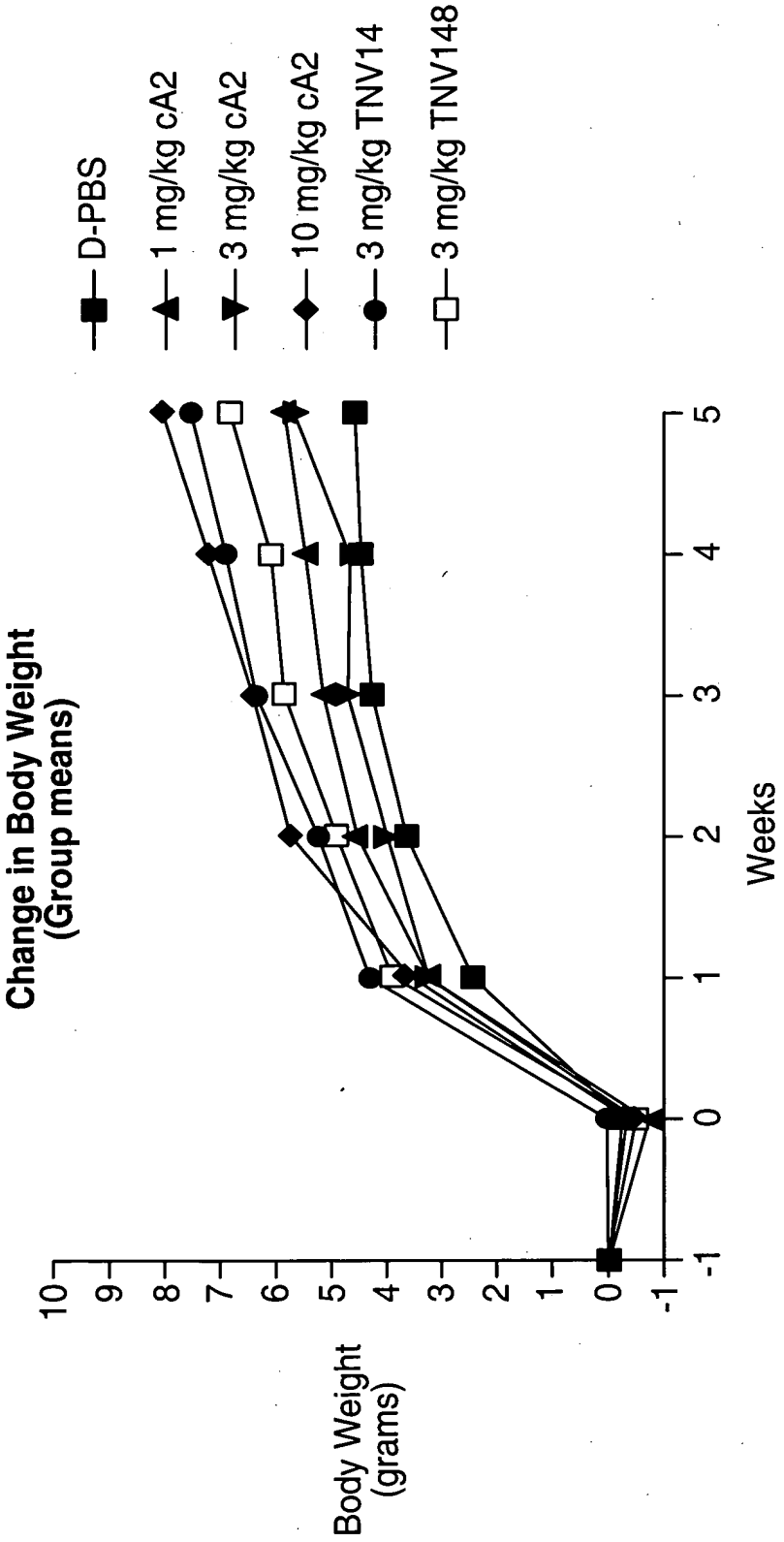

Change in Body Weight
(Group means)
D-PBS
1 mg/kg cA2
3 mg/kg cA2
10 mg/kg cA2
3 mg/kg TNV14
3 mg/kg TNV148
Body Weight
(grams)
10
9
8
7
6
5
4
3
2
1
0
-1
-1
0
1
2
3
4
5
Weeks

FIG. 13A

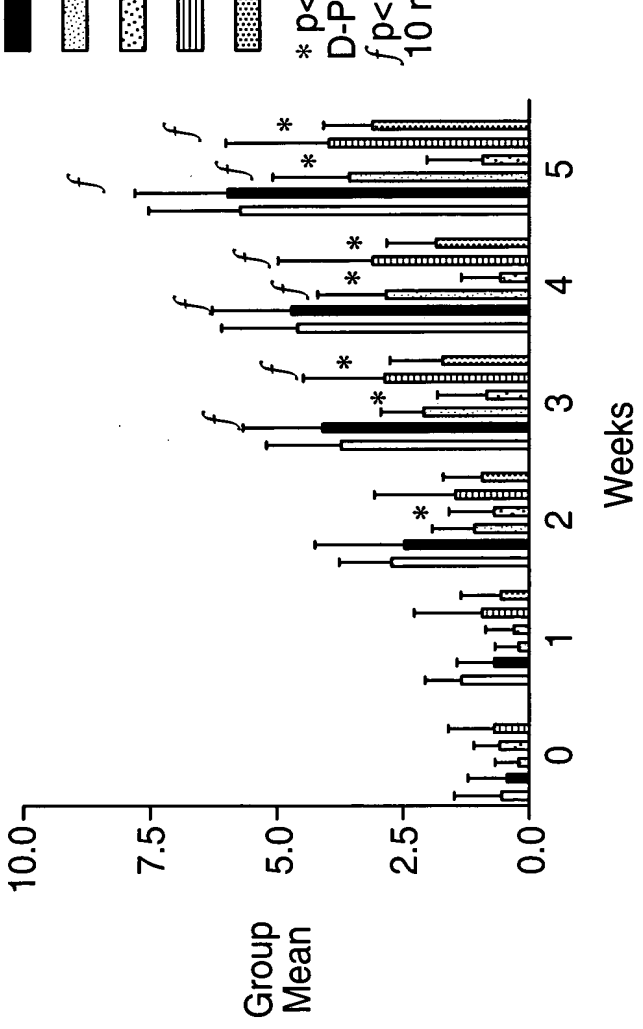
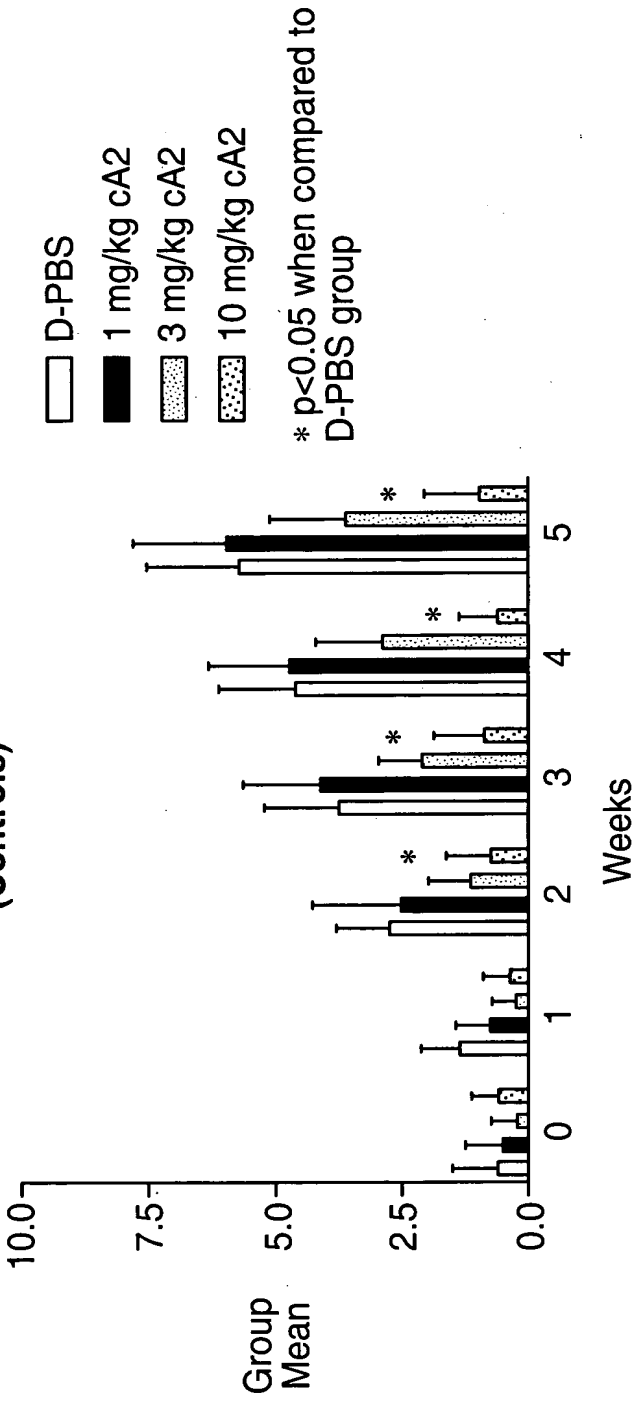

Arthritic Index
D-PBS
1 mg/kg cA2
3 mg/kg cA2
10 mg/kg cA2
3 mg/kg TNV14
3 mg/kg TNV148
* p<0.05 when compared to D-PBS group
f p<0.05 when compared to 10 mg/kg cA2 group
Group Mean
10.0
7.5
5.0
2.5
0.0
0
1
2
3
4
5
Weeks

FIG. 13B


Arthritic Index
(Controls)
D-PBS
1 mg/kg cA2
3 mg/kg cA2
10 mg/kg cA2
* p<0.05 when compared to D-PBS group
Group Mean
10.0
7.5
5.0
2.5
0.0
0
1
2
3
4
5
Weeks

PATENT APPLICATION

FIG. 13C

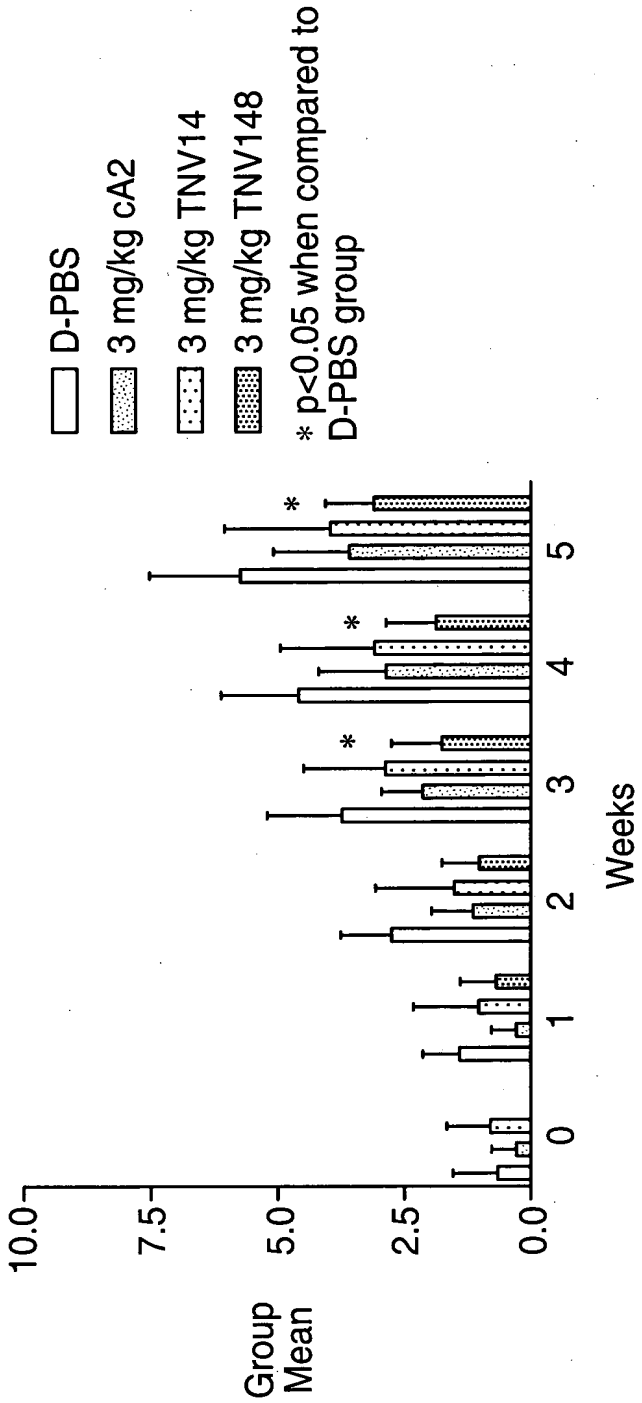


FIG. 14

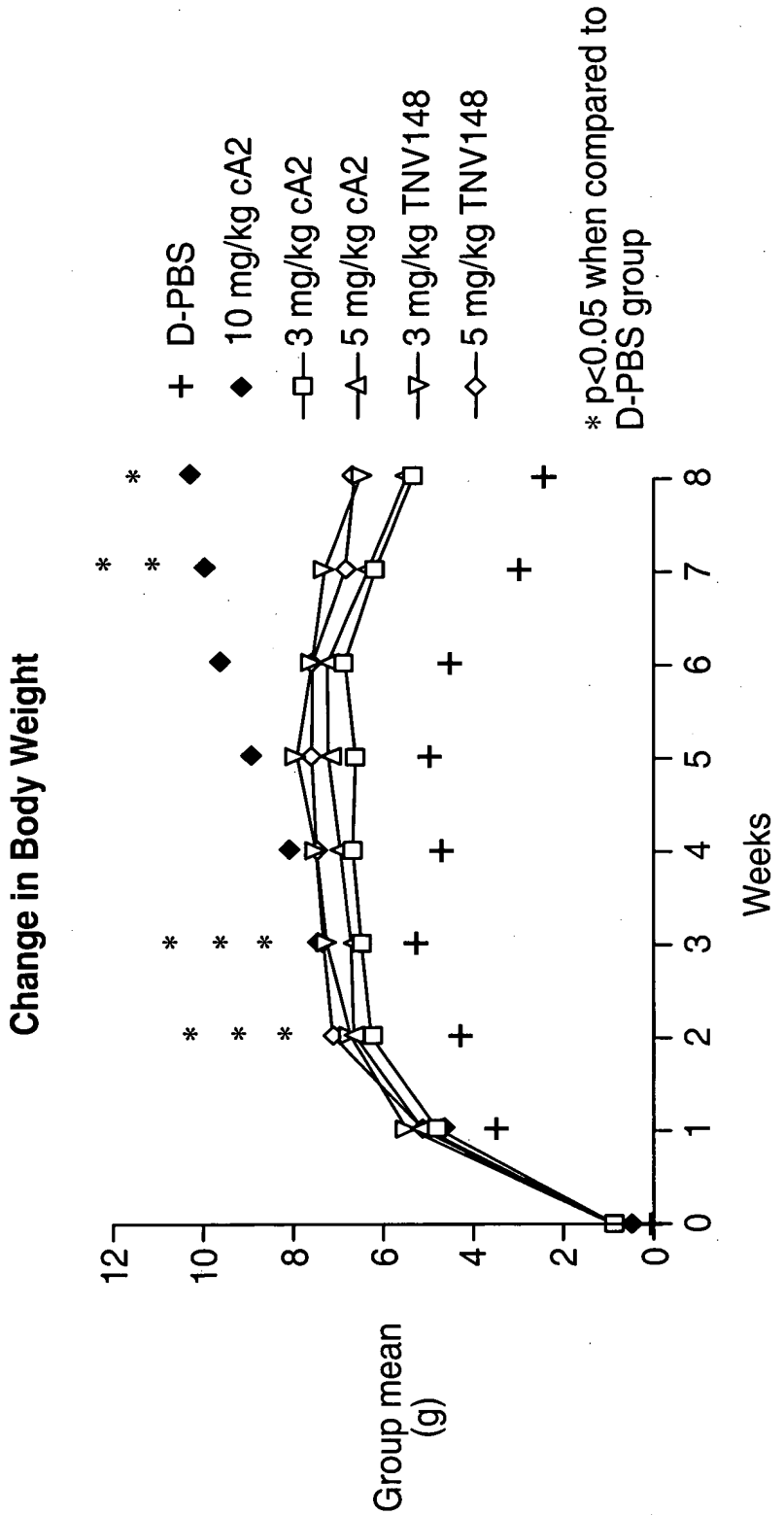

Change in Body Weight
D-PBS
10 mg/kg cA2
3 mg/kg cA2
5 mg/kg cA2
3 mg/kg TNV148
5 mg/kg TNV148
* p<0.05 when compared to D-PBS group
Group mean (g)
Weeks
0
2
4
6
8
10
12
0
1
2
3
4
5
6
7
8

FIG. 15

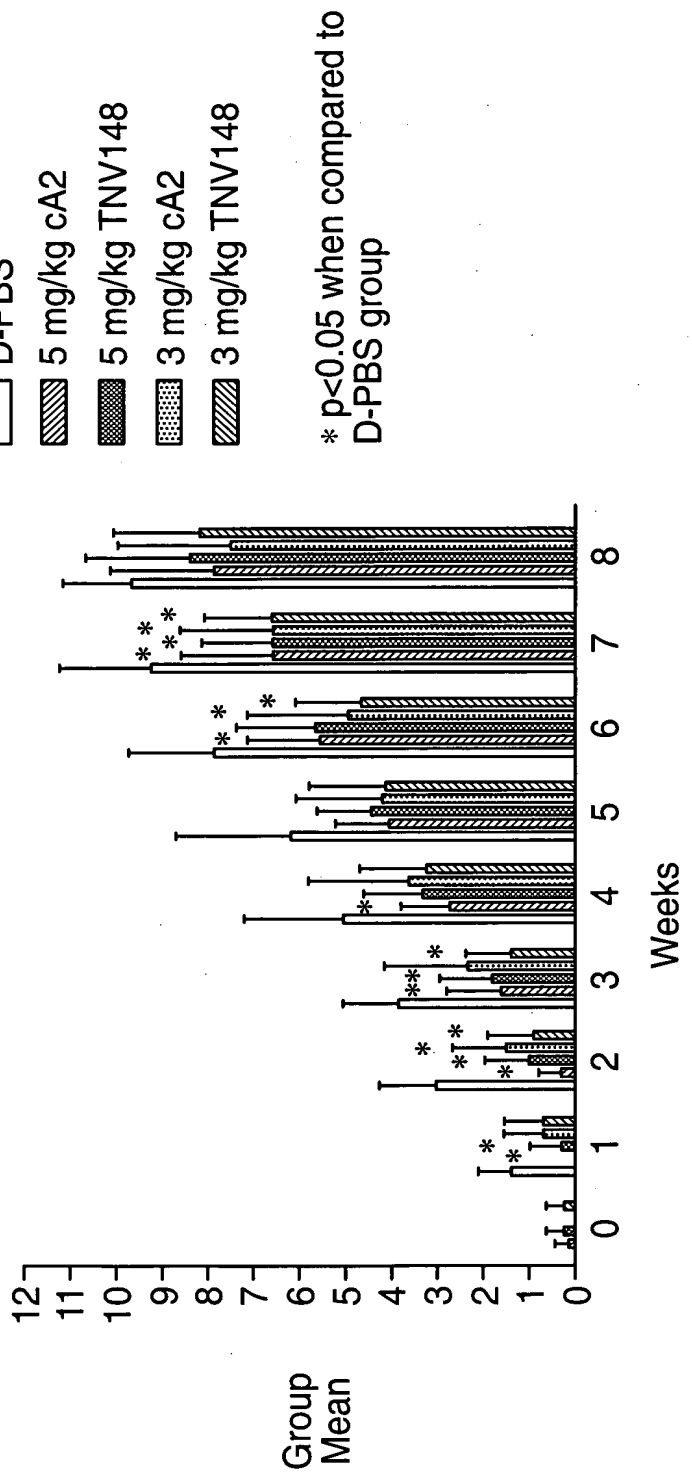

Arthritic Index
D-PBS
5 mg/kg cA2
5 mg/kg TNV148
3 mg/kg cA2
3 mg/kg TNV148
* p<0.05 when compared to D-PBS group
Group Mean
Weeks
0
1
2
3
4
5
6
7
8
9
10
11
12

FIG. 16

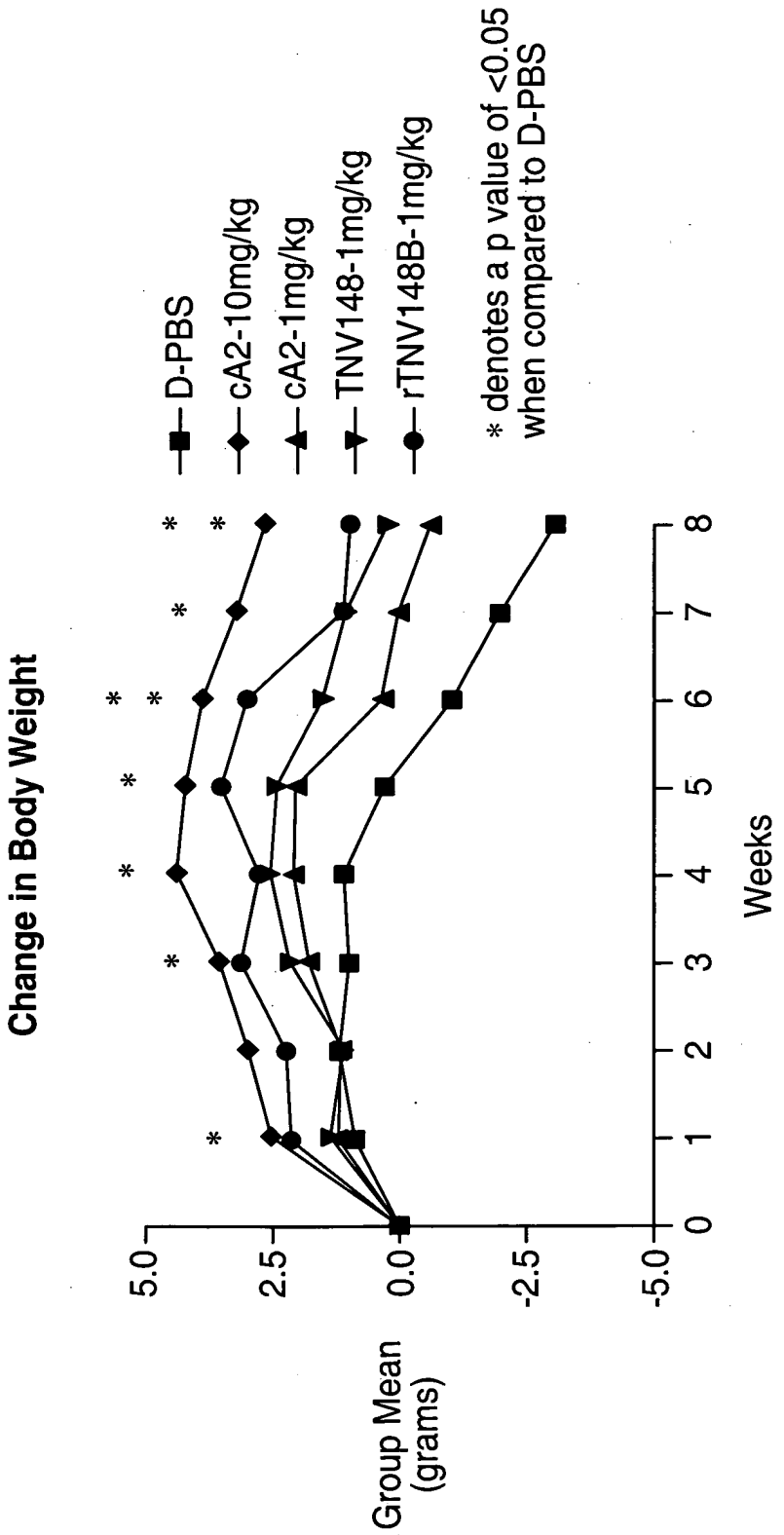
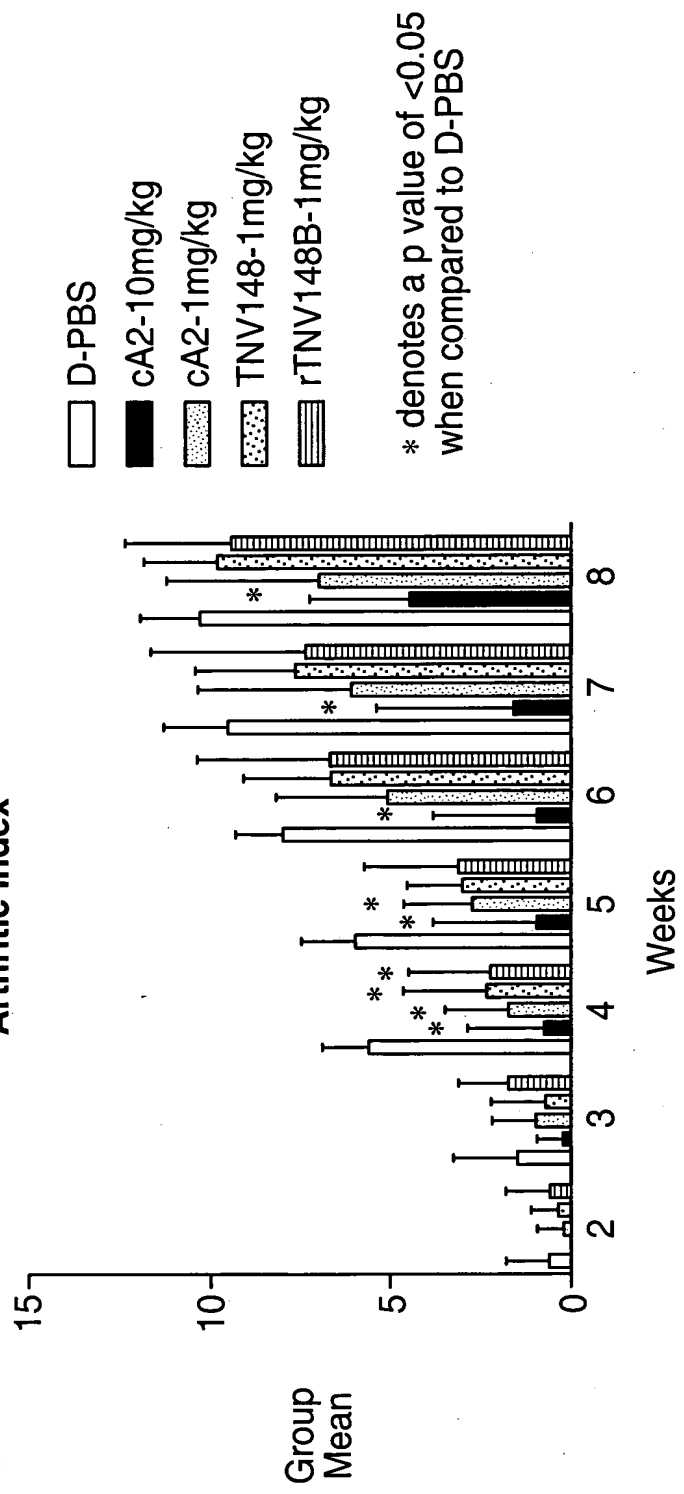

Change in Body Weight
D-PBS
cA2-10mg/kg
cA2-1mg/kg
TNV148-1mg/kg
rTNV148B-1mg/kg
* denotes a p value of <0.05 when compared to D-PBS
Group Mean (grams)
5.0
2.5
0.0
-2.5
-5.0
0
1
2
3
4
5
6
7
8
Weeks

FIG. 17


Arthritic Index
D-PBS
cA2-10mg/kg
cA2-1mg/kg
TNV148-1mg/kg
rTNV148B-1mg/kg
* denotes a p value of <0.05 when compared to D-PBS
Group Mean
0
5
10
15
2
3
4
5
6
7
8
Weeks